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(54) Title: COATING FOR REDUCING THE RATE OF RELEASE OF DRUGS FROM STENTS

(57) Abstract: A stent for delivery of a therapeutic agent is disclosed. The stent includes a polymer coating for reducing the rate of release of the therapeutic agent. The polymer has a crystalline structure wherein the polymer is capable of significantly maintaining the crystalline lattice structure while the therapeutic agent is released from the stent such that the aqueous environment to which the stent is exposed subsequent to the implantation of the stent does not significantly convert the crystalline lattice structure of the polymer to an amorphous structure.

site and thus smaller total levels of medication can be administered in comparison to systemic dosages that often produce adverse or even toxic side effects for the patient.

[0004] One method of medicating a stent involves the use of a polymeric carrier coated onto the surface of the stent. A composition including a solvent, a polymer dissolved in the solvent, and a therapeutic substance dispersed in the blend is applied to the stent by immersing the stent in the composition or by spraying the composition onto the stent. The solvent is allowed to evaporate, leaving on the stent strut surfaces a coating of the polymer and the therapeutic substance impregnated in the polymer.

[0005] Depending on the physiological mechanism targeted, the therapeutic substance may be required to be released at an efficacious concentration for an extended duration of time. Increasing the quantity of the therapeutic substance in the polymeric coating can lead to poor coating mechanical properties, inadequate coating adhesion, and overly rapid rate of release. Increasing the quantity of the polymeric compound by producing a thicker coating can perturb the geometrical and mechanical functionality of the stent as well as limit the procedures for which the stent can be used.

[0006] It is desirable to increase the residence time of a substance at the site of implantation, at a therapeutically useful concentration, without the addition of a greater percentage of the therapeutic substance to the polymeric coating and without the application of a significantly thicker coating.

polymer includes a crystalline structure during the duration of delivery of an active agent from the stent, and the aqueous environment to which the stent is exposed subsequent to the implantation procedure does not significantly change the crystalline structure to an amorphous structure.

[0011] Also disclosed is a stent for delivering a therapeutic agent to an implanted site. The stent includes a radially expandable body structure and a polymeric coating supported by the body structure for extending the residence time of the therapeutic agent at the implanted site. The polymeric coating is made from a hydrophobic polymer having a degree of crystallinity that remains at or above about 10% at least until a significant amount of the therapeutic substance has been released from the stent.

DETAILED DESCRIPTION

Embodiments of the Rate-Reducing Coating

[0012] One mechanism through which the release rate of an active agent from a medical device can be controlled is the crystallinity of the polymer with which the medical device is coated. A polymer in which the molecules are arranged in a highly ordered and regular pattern formed by folding and stacking of the polymer chains is said to be crystalline. By contrast, amorphous polymers have molecules that are arranged randomly with no regularity of orientation with respect to one another. Among the factors that affect polymer crystallinity are the stereoregularity of the polymer, the tacticity of the polymer, the presence of branching, the degree

no intermolecular forces will tend to have random, non-crystalline structures as a result of thermal motion.

[0016] Typically, as the crystallinity of a polymer increases, so too does the polymer's ability to reduce the rate at which an active agent is released from a medical device coated with the polymer. This is because it is more difficult for an active agent to diffuse through a tightly packed, crystalline polymer than a more loosely packed, amorphous polymer. The purpose of the coating of the present invention is to decrease the rate of release of an active agent therefrom. Accordingly, the polymer for forming the rate-reducing coating should be selected to have sufficient crystallinity such that the active agent may not readily diffuse therethrough.

[0017] The degree of crystallinity of the polymer can be measured by the amount of the polymer that is in the form of crystallites or a detectable pattern of crystals as may be observed using conventional techniques such as x-ray diffraction, measurement of specific volume, infrared spectroscopy, and thermal analysis. For use with the embodiments of the present invention, the polymer can have a crystallinity of not less than about 10%, alternatively not less than about 25%. In accordance with another embodiment the degree of crystallinity should not be less than about 50%. When exposed to an aqueous environment such as blood, the polymer can have a crystallinity of not less than about 10%, alternativley not less than 25%. In one example, the polymer can have a crystallinity of at least 50% or at least 25% in an aqueous environment, such as in contact with blood.

("Polymer Handbook", 2nd Ed., Brandrup J. and EH Immergut, ed., Wiley-Interscience, John Wiley & Sons, N.Y. (1975)). Because polymers are typically non-volatile and thus cannot be vaporized without decomposition, the solubility parameter is measured indirectly. Briefly, solvents in which a polymer dissolves without a change in heat or volume are identified. The solubility parameter of the polymer is then defined to be the same as the solubility parameters of the identified solvents.

[0020] As a general rule, the value of the solubility parameter δ is inversely proportional to the degree of hydrophobicity of a polymer. Polymers that are very hydrophobic may have a low solubility parameter value. This general proposition is particularly applicable for polymers having a glass transition temperature below physiological temperature. A polymer that is sufficiently hydrophobic for use in the rate-limiting membrane of the present invention can have a solubility parameter of not more than about 10.7 $(cal/cm^3)^{1/2}$. Representative examples of such crystalline, hydrophobic polymers include polytetrafluoroethylene, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropene, low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, styrenic block copolymers including KRATON™ polymers (available from KRATON™ Polymers, Houston, Texas), ethylene-anhydride copolymers, ethylene-acrylic acid copolymers, poly (vinylidene fluoride), ethylene methacrylic acid copolymers,

capable of significantly dissolving the polymer at the concentration desired in the composition. Examples of solvents include, but are not limited to, dimethylsulfoxide (DMSO), chloroform, acetone, xylene, methanol, ethanol, 1-propanol, tetrahydrofuran, 1-butanone, dimethylformamide, dimethylacetamide, cyclohexanone, ethyl acetate, methylethylketone, propylene glycol monomethylether, isopropanol, isopropanol admixed with water, N-methyl pyrrolidinone, toluene, hexafluoroisopropanol, methylene chloride, hexamethylphosphorous triamide, N-methylmorpholine, trifluoroethanol, formic acid, and phenol. The polymeric compound can be added to the solvent at ambient pressure and under anhydrous atmosphere. The polymeric compound is soluble before crystallization in a solvent system at, for example, temperatures of less than or equal to about 80°C. If necessary, gentle heating and stirring and/or mixing can be employed to effect dissolution of the polymer into the solvent, for example 12 hours in a water bath at about 60°C.

[0023] Application of the composition can be by any conventional method, such as by spraying the composition onto the device or by immersing the device in the composition. Operations such as wiping, centrifugation, blowing, or other web-clearing acts can also be performed to achieve a more uniform coating. Briefly, wiping refers to physical removal of excess composition from the surface of the stent; centrifugation refers to rapid rotation of the stent about an axis of rotation; and blowing refers to application of air at a selected pressure to the deposited composition. Any excess composition can also be vacuumed off of the surface of the device. The solvent is removed from the composition to form the rate-reducing

cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention.

Use of the Rate-Reducing Coating

[0025] In one embodiment, the above-described rate-reducing coating, free from therapeutic substances or active agents, can function as a barrier layer through which an underlying therapeutic substance or active agent must diffuse to be released from a device into a treatment site. The active agent can be carried by the device, such as in porous cavities in the surface of the device, or can be impregnated in a reservoir polymer layer formed beneath the rate-reducing coating. Such a rate-reducing barrier coating can be of any suitable thickness. The thickness of the coating can be from about 0.01 microns to about 20 microns, more narrowly from about 0.1 microns to about 10 microns. By way of example, the rate-reducing barrier coating can have a thickness of about 3 microns.

[0026] In another embodiment, the rate-reducing coating can additionally function as a reservoir for carrying the therapeutic substance or active agent. In such an embodiment, sufficient amounts of an active agent can be dispersed in the blended composition of the suitably crystalline polymer and the solvent. The polymer can comprise from about 0.1% to about 35%, more narrowly from about 2% to about 20% by weight of the total weight of the composition, the solvent can

Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere®, from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as Angiomax ™ (Biogen, Inc., Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an

solvent will be removed from the primer composition but traces or residues can remain blended with the polymer.

[0030] In other embodiments, the crystalline coating can be topcoated with one or more additional coating layers. Such additional coating layers can be for increasing the biocompatibility of the device. For example, in one embodiment, the additional coating layer can be formed from ethylene vinyl alcohol (EVAL), polyethylene glycol, polyethylene oxide, hyaluronic acid, heparin, or heparin derivatives having hydrophobic counterions, thereby providing biocompatibility to the outermost, tissue-contacting surface of the medical device.

[0031] In another embodiment, an additional coating layer can serve as yet another rate-reducing layer. Because the additional rate-reducing layer does not contain active agents, the methods by which such a layer is deposited is not limited to the methods by which the polymer layers having active agents are applied. Therefore, in addition to application by conventional methods, such as by spraying a polymeric composition onto the device or by immersing the device in a polymeric composition, the additional rate-reducing layers can be deposited by physical vapor deposition (PVD) techniques, which are known to one of ordinary skill in the art. Representative examples of barrier materials that can be deposited via PVD techniques include plasma-deposited polymers, parylene C, parylene N, parylene D, perfluoro parylene, tetrafluoro (AF4) parylene, metallic layers, metallic oxides, metal carbides, and metal nitrides.

Methods of Use

expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

EXAMPLES

[0034] The embodiments of the invention will be illustrated by the following set forth prophetic examples, which are being given by way of illustration only and not by way of limitation. All parameters are not to be construed to unduly limit the scope of the embodiments of the invention.

Example 1

[0035] A 2% (w/w) solution of EVAL in dimethylacetamide (DMAC) is applied to a 13 mm Tetra™ stent (available from Guidant Corporation) using an EFD 780S spray device (available from EFD Inc., East Providence, RI) until 50 micrograms of solids have been deposited onto the stent. The stent is baked at 140°C for 60 minutes to form a primer layer on the stent. A solution of 1:9 (w/w) actinomycin D:EVAL and 2% (w/w) EVAL in DMAC is sprayed onto the primered stent until 100 micrograms of solids have been deposited. The stent is baked at 50°C for 2 hours to form an actinomycin D-containing reservoir coating. A 2% (w/w) polyvinylidene fluoride solution in DMAC is sprayed until 300 micrograms of solids have been deposited onto the stent. The stent is baked at 50°C for 2 hours to form a crystalline rate-reducing membrane of polyvinylidene fluoride.

Example 4

[0038] A 2% (w/w) solution of poly(n-butyl methacrylate) in 4:1 (w/w) acetone:cyclohexanone is applied to a 13 mm Tetra™ stent using an EFD 780S spray device until 50 micrograms of solids have been deposited onto the stent. The stent is baked at 70°C for 60 minutes to form a primer layer on the stent. A solution of 1:2 (w/w) etoposide:EVAL and 2% (w/w) EVAL in DMAC is sprayed onto the primered stent until 300 micrograms of solids have been deposited. The stent is baked at 60°C for 2 hours to form an etoposide-containing reservoir coating. A 1.5% (w/w) silicone-urethane Elast-Eon™ 55D (available from Elastomedic Pty Ltd., Australia) solution in 1:1 (w/w) THF:DMAC is sprayed until 300 micrograms of solids have been deposited onto the stent. The stent is baked at 60°C for 2 hours to form a crystalline rate-reducing membrane of silicone-urethane Elast-Eon™ 55D.

[0039] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

polyethylenes having high molecular weights, ethylene-olefin copolymers, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, ethylene-anhydride copolymers, ethylene-acrylic acid copolymers, styrenic block copolymers, ethylene methacrylic acid copolymers, polyurethanes with a polydimethylsiloxane soft segment, poly(vinylidene fluoride-co-hexafluoropropene), poly(vinylidene fluoride), and polycarbonate urethanes.

6. The stent of Claim 1, wherein the polymer is selected from a group of nylon 6, polytetrafluoroethylene, polyetheretherketone, polyimide, polysulfone, ethylene-co-methacrylic acid, ethylene-co-acrylic acid, poly(vinylidene fluoride), poly(vinylidene fluoride-co-hexafluoropropene) and styrenic block copolymers.

7. The stent of Claim 1, wherein the coating contains the therapeutic agent for delivery of the therapeutic agent.

8. The stent of Claim 7, additionally comprising:

a primer layer formed on the surface of the medical device, wherein the coating is formed over the primer layer, and wherein the primer layer acts as an adhesive tie between the coating and the surface of the medical device.

13. The method of Claim 11, wherein the crystallinity of the polymeric material is not less than about 25% during the release of the therapeutic agent from the stent.

14. The method of Claim 11, wherein the polymeric material has a solubility parameter not more than about 10.7 $(cal/cm^3)^{1/2}$.

15. The method of Claim 11, wherein the polymeric material has a melting point greater than or equal to about 135°C at ambient pressure.

16. The method of Claim 11, wherein the polymer is selected from a group of polytetrafluoroethylene, ethylene-tetrafluoroethylene copolymer, fluoroethylene-alkyl vinyl ether copolymer, polyhexafluoropropene, poly(vinylidene fluoride), low density linear polyethylenes having high molecular weights, ethylene-olefin copolymers, styrene-ethylene-styrene block copolymers, styrene-butylene-styrene block copolymers, styrene-ethylene/butylene-styrene block copolymers, styrene-butadiene-styrene block copolymers, styrenic block copolymers, ethylene-anhydride copolymers, ethylene-acrylic acid copolymers, ethylene methacrylic acid copolymers, polyurethanes with a polydimethylsiloxane soft segment, poly(vinylidene fluoride-co-hexafluoropropene), and polycarbonate urethanes.

17. The method of Claim 11, wherein the polymer is selected from a group of nylon 6, polytetrafluoroethylene, polyetheretherketone, polyimide, polysulfone, ethylene-co-methacrylic acid, ethylene-co-acrylic acid,

INTERNATIONAL SEARCH REPORT

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 5 980 972 A (DING NI) 9 November 1999 (1999-11-09) column 3, line 17 - line 51; claims	1-19
X	WO 01 45763 A (ADVANCED CARDIOVASCULAR SYSTEM) 28 June 2001 (2001-06-28) claims; examples	1-19
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

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